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Serum albumin corrected anion gap levels are associated with poor prognosis in patients with acute ischemic stroke

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Acute ischemic stroke (AIS) remains a major cause of global morbidity and mortality. This study aimed to evaluate the role of albumin corrected anion gap (ACAG) as a prognostic marker for AIS patients. We analyzed data from 1014 AIS patients in the MIMIC-IV database, stratifying patients by ACAG levels. Using Cox proportional hazards models, restricted cubic splines, and Kaplan-Meier survival analysis, we assessed the relationship between ACAG and both 30-day and 365-day mortality. Our results show that elevated ACAG levels are significantly associated with higher mortality rates at both time points. The hazard ratios for 30-day and 365-day mortality were 1.07 (95% CI 1.04–1.11, $P < 0.001$) and 1.06 (95% CI 1.03–1.09, $P < 0.001$), respectively. Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) of ACAG for predicting 30-day and 365-day mortality was 0.666 and 0.662, respectively. Subgroup analysis revealed significant interactions with gender and sepsis status. A nomogram incorporating ACAG and other key variables achieved AUCs of 0.748 and 0.765 for predicting 30-day and 365-day mortality, respectively. These findings indicate that elevated ACAG is an independent risk factor for both short-term and long-term mortality in AIS patients. Its incorporation into clinical practice may enhance the ability of clinicians to identify high-risk patients early, enabling timely and targeted interventions.

Keywords Acute ischemic stroke, Albumin corrected anion gap, MIMIC-IV database, Mortality, Prognosis

Acute ischemic stroke (AIS) is the second leading cause of death globally, responsible for 11.6% of total fatalities, placing a substantial burden on healthcare systems and economies[1,2]. Despite advances in therapeutic interventions, the prognosis following AIS often remains poor, particularly in patients with severe ischemic damage[3,4]. Recognizing individuals at increased risk for poor outcomes early on is crucial for improving clinical decision-making and optimizing patient care.

Several prognostic markers have been proposed to predict outcomes in AIS, including inflammatory markers such as C-reactive protein (CRP), metabolic indicators like glucose levels, and oxidative stress-related markers[5–7]. While these biomarkers have shown some predictive value, each has its limitations. For instance, CRP reflects systemic inflammation but may not be specific to ischemic processes in the brain. Similarly, hyperglycemia is common in AIS but can be confounded by stress responses rather than being a direct indicator of stroke severity. Therefore, the search for more reliable and specific prognostic markers remains ongoing.

The anion gap is frequently employed in clinical practice to assess metabolic acidosis and evaluate acid-base balance[8]. However, its levels can be significantly influenced by serum albumin concentrations, especially in critically ill patients with reduced albumin levels[9]. Albumin, the main negatively charged protein in plasma, normally contributes to the anion gap. When albumin levels decrease, the reduction in negative charges lowers the anion gap, which can obscure the detection of metabolic acidosis. In such cases, the traditional anion gap may not accurately reflect the underlying metabolic disturbances.

To address this limitation, the albumin corrected anion gap (ACAG) was introduced[10]. By adjusting the anion gap for serum albumin levels, ACAG provides a more accurate representation of metabolic disturbances[10,11]. The corrected anion gap is calculated by adding a correction factor based on albumin concentrations to the

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traditional anion gap, accounting for hypoalbuminemia. This adjustment helps to better reflect underlying metabolic imbalances, especially in critically ill patients, where albumin levels are commonly reduced. ACAG has been associated with prognosis and disease severity in various conditions, including sepsis, acute myocardial infarction (AMI), and acute kidney injury (AKI)[11–13]. Despite these findings, its role in predicting outcomes in AIS patients has yet to be explored. AIS is a complex condition involving ischemic brain damage along with systemic responses such as inflammation, oxidative stress, and metabolic disruptions. Given this complexity, ACAG could potentially serve as a valuable prognostic tool by providing a more accurate assessment of acid-base imbalances particularly in cases of hypoalbuminemia. However, it remains unknown whether ACAG reliably predicts adverse outcomes in AIS patients or whether it offers added prognostic value beyond existing clinical scoring systems.

This study aims to evaluate the association between serum ACAG levels and clinical outcomes in AIS patients, with the goal of determining its potential as a predictive tool for poor prognosis.

Materials and methods

Database introduction

This study used data from the MIMIC-IV database, a comprehensive and publicly accessible critical care dataset sourced from the United States (Beth Israel Deaconess Medical Center, Boston, Massachusetts). The database contains de-identified health records from over 60,000 ICU admissions between 2008 and 2019[14]. As the dataset represents a diverse patient population in the United States, it includes individuals from multiple ethnic and racial backgrounds. The corresponding author (Guangdong Wang, Record ID: 60106105) obtained access to the database after completing the required data use certification.

Population selection criteria

The study cohort was derived from the MIMIC-IV 2.2 database, which contained 50,920 first-time ICU admissions. AIS patients were identified based on ICD-9 and ICD-10 codes, including I63, 43,391, 43,321, 43,331, 43,301, 43,381, 43,401, 43,411, and 43,311, yielding an initial cohort of 2416 patients. The number of patients associated with each ICD code is provided in Supplementary Table S1. The following exclusion criteria were applied: patients < 18 years old ($n = 0$), those with an ICU stay < 24 h ($n = 240$), individuals lacking available ACAG data ($n = 1088$), and patients with end-stage renal disease or liver cirrhosis ($n = 74$) were excluded. Following these exclusions, 1014 patients remained for the final analysis (Fig. 1).

Data extraction and ACAG

The following data were extracted: demographics, including age, gender, and race; vital signs, such as heart rate, mean blood pressure (MBP), oxygen saturation (SpO2), and body temperature; and comorbidities, including AMI, heart failure, diabetes, renal disease, AKI, and sepsis. Laboratory measurements included white blood cell (WBC) count, red cell distribution width (RDW), platelet, hemoglobin, albumin, blood urea nitrogen (BUN), creatinine, glucose, potassium, sodium, and the anion gap. The severity of illness was assessed using the Sequential Organ Failure Assessment (SOFA) score and the Glasgow Coma Scale (GCS). Therapeutic interventions documented included the use of vasopressors, ventilation, continuous renal replacement therapy (CRRT), anticoagulants, antiplatelet therapy, recombinant tissue plasminogen activator (rt-PA), and thrombectomy. The

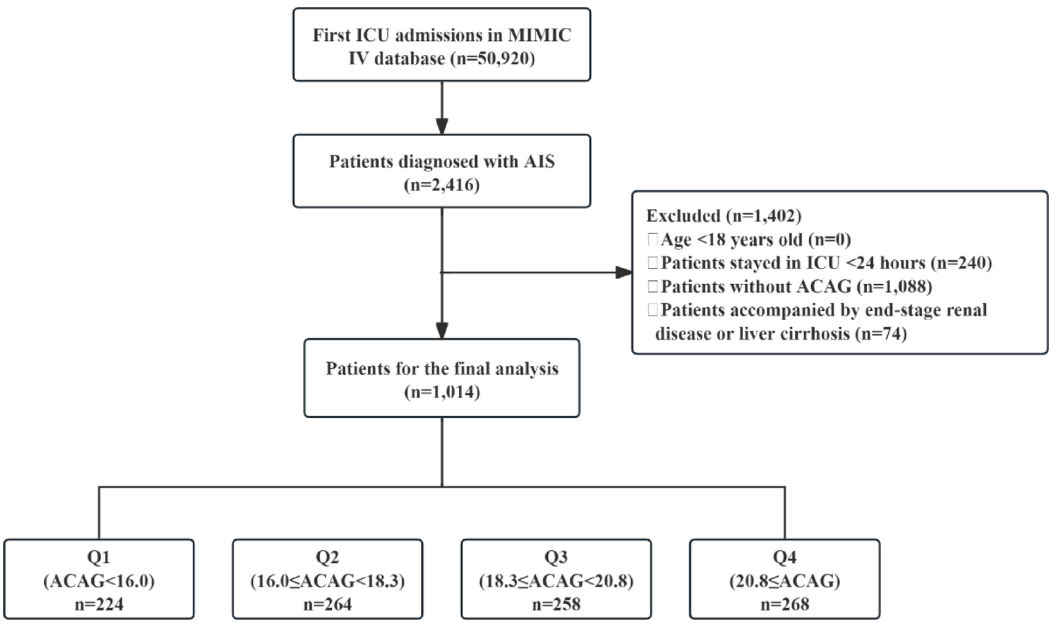

Fig. 1. The flowchart of patient selection. Abbreviations: AIS, acute ischemic stroke; ICU, intensive care unit; ACAG, albumin corrected anion gap.

ACAG was calculated using the formula: ACAG = anion gap + 2.5 × (4.4 − albumin (g/dL))[15,16]. SQL queries were used to collect all relevant data, and laboratory parameters were obtained during the first day following the patient's ICU admission.

Groups and outcomes

Patients were categorized into four groups according to their ACAG levels: Q1 (ACAG < 16.0, $n = 224$), Q2 (16.0 ≤ ACAG < 18.3, $n = 264$), Q3 (18.3 ≤ ACAG < 20.8, $n = 258$), and Q4 (ACAG ≥ 20.8, $n = 268$).

The primary outcomes were 30-day and 365-day mortality. Secondary outcomes included ventilator-free days within 14 days (VFD-14), hospital and ICU stay, hospital and ICU mortality.

Statistical analysis

To describe the baseline characteristics across different ACAG levels, appropriate statistical methods, including the Kruskal-Wallis H test, chi-square test, or ANOVA, were employed to assess clinical features and overall mortality across ACAG quartiles. Normally distributed variables were expressed as mean ± SD, non-normally distributed variables as median (IQR), and categorical variables as percentages.

Least absolute shrinkage and selection operator (LASSO) regression analysis was used to select variables associated with 30-day outcome, and a Cox proportional hazards model was constructed to evaluate the association between ACAG and 30-day and 365-day mortality. To reduce confounding effects between ACAG and outcomes, three models were developed to calculate hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality, with trend tests applied. Model 1 was adjusted for age, gender, and race. Model 2 was adjusted for Model 1 variables plus heart rate, SpO2, GCS, sepsis, WBC, RDW, hemoglobin, BUN, and glucose. Model 3 was further adjusted for Model 2 variables plus ventilation, vasopressor use, antiplatelet use, and rt-PA administration. The lowest ACAG quartile was used as the reference group for all models.

Restricted cubic spline (RCS) analysis was performed to further clarify the relationship between ACAG and mortality. Additionally, Kaplan-Meier survival curves and the log-rank test were used to evaluate differences in primary endpoints across patients with different ACAG levels. Receiver operating characteristic (ROC) curves were applied to assess the predictive accuracy. Subgroup and interaction analyses were performed according to age (< 65 or ≥ 65 years), gender, race (other or white), SOFA score (< 5 or ≥ 5), AKI status (no or yes), presence of sepsis (no or yes), rt-PA administration (no or yes), and thrombectomy (no or yes). A nomogram prediction model was constructed based on the ACAG and additional risk factors. To evaluate the robustness of the findings, sensitivity analyses were conducted by sequentially excluding participants with missing data, ICU stays of less than 48 h, and those who had undergone thrombectomy.

In all analyses, the percentage of missing data for covariates was less than 1%, as shown in Table S2, and missing values were imputed using the mean or median, as appropriate. Data analysis was carried out using R software version 4.4.1 and Free Statistics software version 2.0. P-values < 0.05 were considered significant.

Results

Patient characteristics

A total of 1,014 patients were included in the study, with a mean age of 68.7 ± 15.9 years. No significant age differences were found between the groups ($P = 0.635$). Gender and race distributions were also similar ($P = 0.129$). SOFA scores increased significantly with higher ACAG ($P < 0.001$), though GCS scores did not differ ($P = 0.851$). Comorbidities including AMI, heart failure, diabetes, AKI, and sepsis were more common in groups with higher ACAG levels ($P < 0.05$). Laboratory values, including WBC, RDW, hemoglobin, albumin, BUN, creatinine, glucose, and anion gap, also differed significantly ($P < 0.001$). Vasopressor use, ventilation, CRRT, and rt-PA were more frequent in higher ACAG groups ($P < 0.05$), while anticoagulant use showed less variation ($P > 0.05$). Patients with higher ACAG levels had worse outcomes, including VFD-14, longer hospital and ICU stays, and higher mortality ($P < 0.001$ for all) (Table 1).

Association between ACAG and all-cause mortality

Table 2 shows a significant association between ACAG levels and mortality in AIS patients. For 30-day mortality, the percentage of non-survivors increased from 4.3% in Q1 to 40.9% in Q4 ($P < 0.001$). Similarly, for 365-day mortality, non-survivors rose from 7.4% in Q1 to 45.7% in Q4 ($P < 0.001$). Both 30-day and 365-day mortality exhibited a significant trend across ACAG quartiles (P for trend < 0.001).

LASSO regression, using the optimal penalty parameter at λ.min, identified 16 candidate variables associated with 30-day mortality (Figure S1). These variables, along with race, were incorporated into the Cox regression analysis. As indicated in Table 3, ACAG showed a significant association with both 30-day and 365-day mortality across all models. For 30-day mortality, the HRs for ACAG were 1.12 (95% CI 1.09–1.15, $P < 0.001$) in Model 1, 1.08 (95% CI 1.05–1.11, $P < 0.001$) in Model 2, and 1.07 (95% CI 1.04–1.11, $P < 0.001$) in Model 3. Similarly, for 365-day mortality, the HRs for ACAG were 1.12 (95% CI 1.09–1.14, $P < 0.001$) in Model 1, 1.07 (95% CI 1.04–1.10, $P < 0.001$) in Model 2, and 1.06 (95% CI 1.03–1.09, $P < 0.001$) in Model 3.

The RCS revealed a non-linear association between ACAG levels and the risk of 30-day and 365-day mortality, with increasing risk observed at higher ACAG concentrations (P for non-linearity < 0.01; Fig. 2).

Kaplan–Meier survival curve

Kaplan–Meier survival curves demonstrated that higher ACAG levels were linked to reduced survival probabilities (Fig. 3). Q1 had the highest survival, while Q4 had the lowest at 30 and 365 days, with significant differences between quartiles ($P < 0.001$).

Variables	Total ($n=1,014$)	Q1 ($n=224$) ACAG < 16.0	Q2 ($n=264$) 16.0 ≤ ACAG < 18.3	Q3 ($n=258$) 18.3 ≤ ACAG < 20.8	Q4 ($n=268$) ACAG > 20.8	*P*-value
Age (year)	68.7 ± 15.9	67.5 ± 15.0	69.0 ± 16.5	69.1 ± 16.0	69.1 ± 16.0	0.635
Gender, n (%)						0.129
Female	526 (51.9)	103 (46)	138 (52.3)	133 (51.6)	152 (56.7)	
Male	488 (48.1)	121 (54)	126 (47.7)	125 (48.4)	116 (43.3)	
Race, n (%)						0.68
Other	434 (42.8)	95 (42.4)	110 (41.7)	106 (41.1)	123 (45.9)	
White	580 (57.2)	129 (57.6)	154 (58.3)	152 (58.9)	145 (54.1)	
Vital signs						
Heart rate (bpm)	83 (71, 97)	77 (66, 86)	80 (68, 94)	85 (73, 97)	91 (78, 105)	< 0.001
MBP (mmHg)	92 (80, 105)	93 (81, 106)	94 (82, 105)	91 (78, 103)	90 (78, 106)	0.123
SpO2 (%)	98 (96, 100)	98 (97, 100)	98 (96, 100)	98 (96, 100)	98 (95, 100)	0.015
Temperature (℃)	36.8 (36.5, 37.1)	36.8 (36.5, 37.1)	36.8 (36.6, 37.1)	36.8 (36.5, 37.2)	36.8 (36.4, 37.1)	0.389
Score system, points						
SOFA	3 (2, 6)	3 (2, 4)	3 (1, 4)	3 (2, 5)	5 (3, 8)	< 0.001
GCS	14 (11, 15)	14 (12, 15)	14 (12, 15)	14 (10, 15)	14 (11, 15)	0.851
Comorbidity disease						
AMI, n (%)	193 (19.0)	34 (15.2)	42 (15.9)	46 (17.8)	71 (26.5)	0.003
Heart failure, n (%)	280 (27.6)	46 (20.5)	59 (22.3)	79 (30.6)	96 (35.8)	< 0.001
Diabetes, n (%)	324 (32.0)	53 (23.7)	79 (29.9)	88 (34.1)	104 (38.8)	0.003
Renal disease, n (%)	180 (17.8)	24 (10.7)	46 (17.4)	46 (17.8)	64 (23.9)	0.002
AKI, n (%)	808 (79.7)	168 (75)	185 (70.1)	214 (82.9)	241 (89.9)	< 0.001
Sepsis, n (%)	512 (50.5)	81 (36.2)	114 (43.2)	136 (52.7)	181 (67.5)	< 0.001
Laboratory results						
WBC (k/uL)	10.3 (7.8, 13.8)	9.1 (7.2, 11.6)	9.8 (7.7, 12.4)	10.4 (8.0, 13.7)	12.5 (8.7, 16.9)	< 0.001
RDW (%)	14.0 (13.2, 15.2)	13.7 (13.1, 14.6)	14.0 (13.2, 14.9)	14.1 (13.2, 15.1)	14.4 (13.4, 16.0)	< 0.001
Platelet (k/uL)	206 (157, 263.8)	205 (160.8, 257)	203.5 (160, 253.2)	211 (157, 264)	202 (145, 285)	0.883
Hemoglobin (g/dL)	11.6 ± 2.3	12.0 ± 2.2	11.8 ± 2.1	11.5 ± 2.4	11.2 ± 2.6	< 0.001
Albumin (g/dL)	3.4 (3.0, 3.8)	3.7 (3.3, 4.0)	3.6 (3.1, 3.9)	3.4 (2.9, 3.8)	3.1 (2.6, 3.5)	< 0.001
BUN (mg/dL)	18 (13, 26)	15 (11, 21)	17 (12, 23)	18 (13, 27)	23 (16, 43)	< 0.001
Creatinine (umol/L)	0.9 (0.7, 1.3)	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	1.2 (0.8, 1.8)	< 0.001
Glucose (mg/dL)	124 (102, 158)	115 (99, 139)	118 (101, 144)	129 (105, 161)	139 (104, 198)	< 0.001
Potassium (mEq/L)	4.1 (3.8, 4.5)	4.1 (3.9, 4.4)	4.0 (3.7, 4.4)	4.1 (3.8, 4.5)	4.1 (3.8, 4.6)	0.185
Sodium (mEq/L)	140 (137, 142)	140 (138, 142)	139 (137, 142)	139 (136, 142)	139 (136, 142)	0.157
Anion gap (mmol/L)	15 (13, 17)	12 (11, 13)	14 (13, 15)	16 (14, 17)	19 (17, 21)	< 0.001
Therapies						
Vasopressor use, n (%)	334 (32.9)	52 (23.2)	62 (23.5)	85 (32.9)	135 (50.4)	< 0.001
Ventilation, n (%)	696 (68.6)	127 (56.7)	170 (64.4)	181 (70.2)	218 (81.3)	< 0.001
CRRT, n (%)	43 (4.2)	1 (0.4)	6 (2.3)	9 (3.5)	27 (10.1)	< 0.001
Anticoagulant use, n (%)	861 (84.9)	187 (83.5)	215 (81.4)	224 (86.8)	235 (87.7)	0.159
Antiplatelet use, n (%)	642 (63.3)	148 (66.1)	178 (67.4)	166 (64.3)	150 (56)	0.029
rt-PA use, n (%)	88 (8.7)	19 (8.5)	13 (4.9)	25 (9.7)	31 (11.6)	0.049
Thrombectomy, n (%)	98 (9.7)	27 (12.1)	25 (9.5)	27 (10.5)	19 (7.1)	0.296
Outcomes						
VFD-14 (day)	12.9 (9.0, 14.0)	13.7 (10.7, 14.0)	13.0 (10.0, 14.0)	12.8 (8.7, 14.0)	11.7 (7.4, 13.7)	< 0.001
Hospital stay (day)	10.7 (5.6, 19.5)	8.3 (4.7, 15.7)	8.6 (4.7, 16.3)	12.6 (6.7, 21.1)	13.1 (6.4, 22.4)	< 0.001
ICU stay (day)	4.9 (2.4, 9.8)	3.8 (2.1, 7.5)	4.3 (2.0, 8.7)	5.2 (2.4, 10.7)	6.4 (3.0, 12.4)	< 0.001
Hospital mortality, n (%)	191 (18.8)	16 (7.1)	44 (16.7)	51 (19.8)	80 (29.9)	< 0.001
ICU mortality, n (%)	130 (12.8)	14 (6.2)	26 (9.8)	36 (14)	54 (20.1)	< 0.001

Table 1. Baseline characteristics of patients. ACAG, albumin corrected anion gap; MBP, mean blood pressure; SpO2, saturation of peripheral oxygen; SOFA, sequential organ failure assessment; GCS, Glasgow coma scale; AMI, acute myocardial infarction; AKI, acute kidney injury; WBC, white blood cell; RDW, red blood cell distribution width; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; rt-PA, recombinant tissue plasminogen activator; VFD-14, ventilator free days in 14 days; ICU, intensive care unit.

Quartiles	30-day mortality				365-day mortality			
	Survivors (n = 756)	Non-survivors (n = 258)	χ^2	*P*-value	Survivors (n = 618)	Non-survivors (n = 396)	χ^2	*P*-value
Q1 (ACAG < 16.0)	156 (95.7)	7 (4.3)	69.633	< 0.001	151 (92.6)	12 (7.4)	64.988	< 0.001
Q2 (16.0 ≤ ACAG < 18.3)	136 (84.5)	25 (15.5)			126 (78.3)	35 (21.7)		
Q3 (18.3 ≤ ACAG < 20.8)	123 (75.9)	39 (24.1)			114 (70.4)	48 (29.6)		
Q4 (ACAG > 20.8)	97 (59.1)	67 (40.9)			89 (54.3)	75 (45.7)		
P for trend				< 0.001				< 0.001

Table 2. All-cause mortality in patients with AIS between the ACAG quartiles. ACAG, albumin corrected anion gap; AIS, acute ischemic stroke.

Variable	Model 1		Model 2		Model 3	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
30-day mortality						
ACAG (continuous)	1.12 (1.09–1.15)	< 0.001	1.08 (1.05–1.11)	< 0.001	1.07 (1.04–1.11)	< 0.001
ACAG (quartiles)						
Q1 (ACAG < 16.0)	1(ref)		1(ref)		1(ref)	
Q2 (16.0 ≤ ACAG < 18.3)	1.84 (1.15–2.94)	0.011	1.69 (1.05–2.71)	0.03	1.70 (1.06–2.72)	0.029
Q3 (18.3 ≤ ACAG < 20.8)	2.51 (1.60–3.94)	< 0.001	2.09 (1.32–3.30)	0.002	2.12 (1.34–3.34)	0.001
Q4 (ACAG > 20.8)	3.96 (2.57–6.09)	< 0.001	2.66 (1.68–4.22)	< 0.001	2.51 (1.58–3.98)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
365-day mortality						
ACAG (continuous)	1.12 (1.09–1.14)	< 0.001	1.07 (1.04–1.10)	< 0.001	1.06 (1.03–1.09)	< 0.001
ACAG (quartiles)						
Q1 (ACAG < 16.0)	1(ref)		1(ref)		1(ref)	
Q2 (16.0 ≤ ACAG < 18.3)	1.68 (1.18–2.40)	0.004	1.57 (1.09–2.24)	0.014	1.58 (1.10–2.26)	0.013
Q3 (18.3 ≤ ACAG < 20.8)	2.34 (1.66–3.29)	< 0.001	1.96 (1.38–2.77)	< 0.001	2.00 (1.41–2.83)	< 0.001
Q4 (ACAG > 20.8)	3.38 (2.43–4.70)	< 0.001	2.26 (1.58–3.22)	< 0.001	2.13 (1.50–3.04)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Table 3. Cox proportional hazard model assessing all-cause mortality in patients with AIS. Model 1: adjusted for age, gender and race. Model 2: adjusted for Model 1 plus heart rate, SpO2, GCS, sepsis, WBC, RDW, hemoglobin, BUN, glucose. Model 3: adjusted for Model 2 plus ventilation, vasopressor use, antiplatelet use, rt-PA use. ACAG, albumin corrected anion gap; AIS, acute ischemic stroke; SpO2, saturation of peripheral oxygen; GCS, Glasgow coma scale; WBC, white blood cell; RDW, red blood cell distribution width; BUN, blood urea nitrogen; rt-PA, recombinant tissue plasminogen activator.

Comparison of predictive values of different indicators

As shown in Fig. 4; Table 4, ACAG demonstrated higher predictive value for both 30-day and 365-day mortality compared to anion gap and albumin alone. For 30-day mortality, ACAG demonstrated an AUC of 0.666 (95% CI 0.629–0.703), surpassing the performance of anion gap (AUC = 0.618) and albumin (AUC = 0.629). Similarly, for 365-day mortality, ACAG had an AUC of 0.662 (95% CI 0.628–0.795), outperforming both anion gap (AUC = 0.606) and albumin (AUC = 0.636). The combination of ACAG and SOFA further improved the predictive performance, achieving the highest AUCs for both 30-day (0.691) and 365-day (0.698) mortality.

Subgroup analysis

Subgroup analysis revealed significant interactions between ACAG and 30-day mortality for gender ($P = 0.015$) and sepsis ($P = 0.018$). No significant interactions were observed in other subgroups, such as age, race, SOFA score, AKI status, rt-PA administration, and thrombectomy status (Fig. 5).

Predictor screening and construction of nomogram model

To construct a clinically applicable prediction model, LASSO regression with λ.1se was used to identify the five most robust predictors: age, SOFA score, ACAG, presence of sepsis, and use of vasoactive drugs. These variables were used to develop a nomogram for individualized prediction of 30-day and 365-day survival (Fig. 6). The model's performance was assessed using ROC analysis, demonstrating good discrimination with an AUC of 0.748 (95% CI 0.716–0.781) for 30-day mortality and 0.765 (95% CI 0.736–0.794) for 365-day mortality (Figure S2), indicating considerable predictive accuracy.

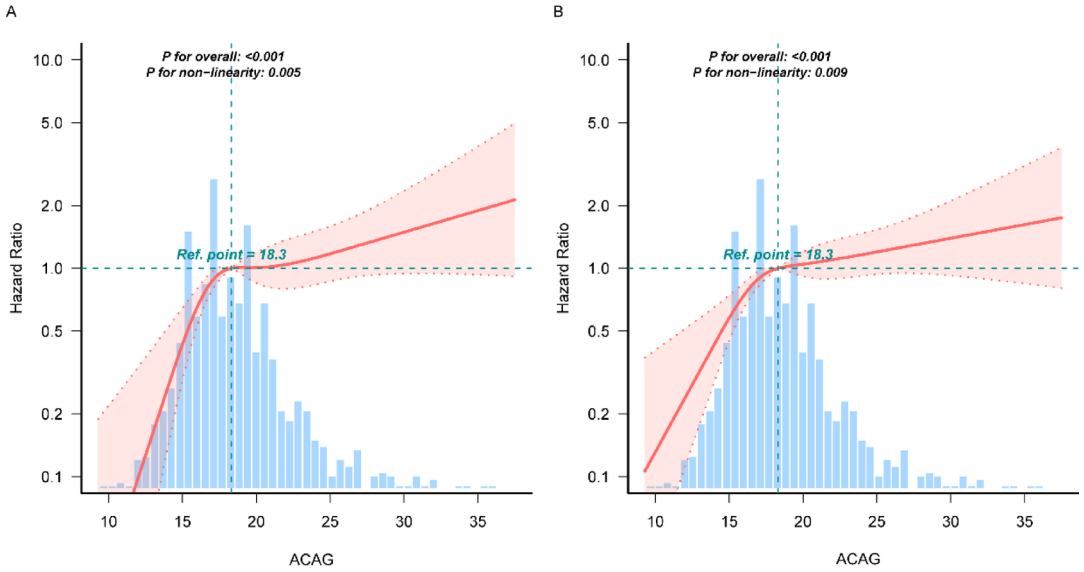

Fig. 2. Restricted cubic spline analysis of the relationship between ACAG and the risk of (**A**) 30-day and (**B**) 365-day all-cause mortality.

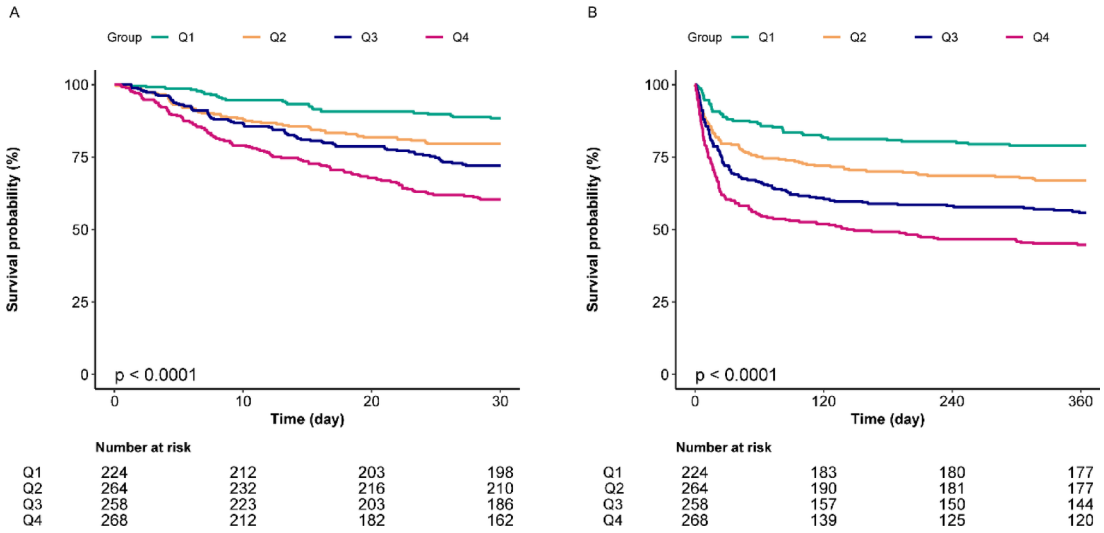

Fig. 3. Kaplan-Meier Survival curves for the cumulative survival rates at 30-day (**A**) and 360-day (**B**) across different ACAG quartiles.

Sensitivity analysis

Three sensitivity analyses were performed. In the first, we excluded patients with missing data, reducing the cohort to 999 patients. In the second analysis, patients with an ICU stay < 48 h were excluded, leaving 827 patients for evaluation. Finally, patients who underwent thrombectomy were excluded, resulting in 916 patients for the final analysis. In all three sensitivity analyses, the results remained statistically significant, confirming the stability of our findings, as shown in Tables S3, S4, and S5.

Discussion

In this study, we found a significant association between ACAG and mortality in AIS patients. Our results indicate that elevated ACAG independently predicts both short-term and long-term mortality. Notably, the predictive value of ACAG surpassed that of the traditional anion gap, suggesting that ACAG may be a more reliable marker of metabolic disturbances in this critically ill population. The nomogram model including ACAG and other key risk factors displayed considerable predictive value for mortality. These findings emphasize ACAG's potential as a valuable prognostic biomarker in AIS, addressing a crucial gap in current patient management where accurate prognostic tools remain limited.

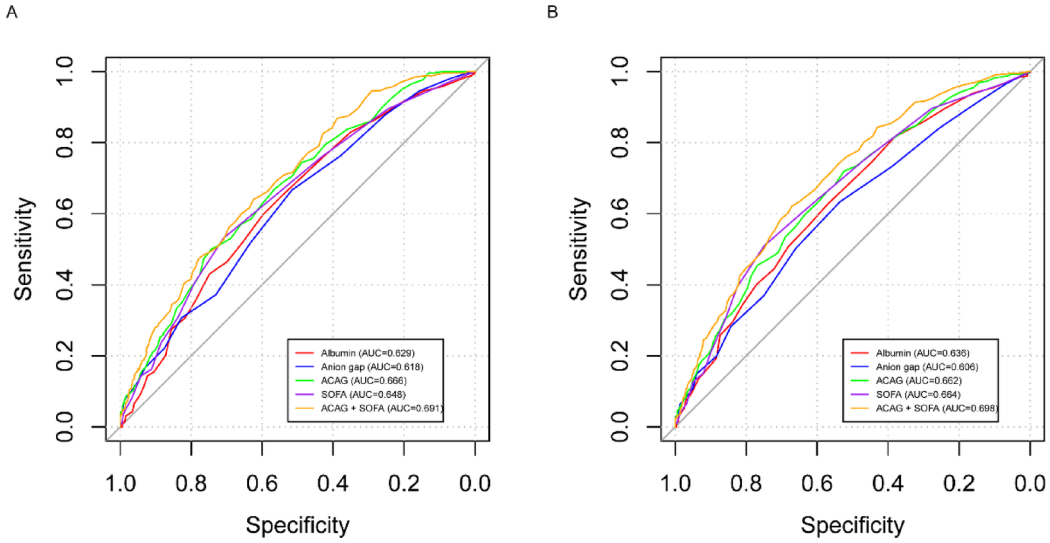

Fig. 4. ROC curves for predicting 30-day (**A**) and 365-day (**B**) mortality using different prognostic markers. Abbreviations: ACAG, albumin corrected anion gap; SOFA, Sequential Organ Failure Assessment; AUC, area under the curve.

Prognostic marker	Cut-off	Sensitivity	Specificity	AUC (95% CI)
30-day mortality				
Albumin	3.45	0.65	0.54	0.629 (0.590–0.667)
Anion gap	14.5	0.67	0.52	0.618 (0.579–0.659)
ACAG	19.9	0.50	0.74	0.666 (0.629–0.703)
SOFA	4	0.53	0.71	0.648 (0.610–0.686)
ACAG + SOFA		0.59	0.68	0.691 (0.655–0.727)
365-day mortality				
Albumin	3.75	0.82	0.38	0.636 (0.601–0.670)
Anion gap	14.5	0.63	0.54	0.606 (0.571–0.642)
ACAG	17.6	0.72	0.52	0.662 (0.628–0.695)
SOFA	4	0.51	0.75	0.664 (0.630–0.798)
ACAG + SOFA		0.63	0.67	0.698 (0.666–0.731)

Table 4. Prognostic accuracy of markers for 30-day and 365-day mortality. ACAG, albumin corrected anion gap; SOFA, sequential organ failure assessment; AUC, area under the curve.

The relevance of ACAG as a prognostic biomarker is supported by prior studies in other critical conditions. In patients with AMI, ACAG was associated with 360-day mortality (HR 1.42, 95% CI 1.21–1.68), and its predictive accuracy (AUC = 0.651) surpassed that of AG (AUC = 0.609)[12]. Similarly, in sepsis patients, ACAG demonstrated higher prognostic ability for hospital mortality, with AUCs of 0.689 before propensity score matching (PSM) and 0.644 after PSM[11]. In patients with AKI requiring CRRT, those with ACAG(> 20 mmol/L) had significantly higher ICU mortality (HR 2.85, 95% CI 1.72–4.73)[16]. In acute pancreatitis, patients with elevated ACAG (> 19.03 mmol/L) had significantly higher in-hospital mortality (HR 3.46, 95% CI 1.75–6.84)[17]. Although a recent study by Chen et al. also explored the association between ACAG and outcomes in ischemic stroke using the same MIMIC-IV database[18], key differences highlight the novelty of our work. Their analysis focused primarily on severe disorders of consciousness (SDOC) and in-hospital mortality. In contrast, our study emphasized long-term follow-up and introduced several methodological innovations, including direct comparisons among ACAG, anion gap, and albumin, evaluation of combined ACAG-SOFA predictive utility, and construction of a nomogram for individualized mortality prediction. These distinctions underscore the added value of our study in addressing current gaps in AIS risk stratification.

The mechanisms by which an elevated ACAG correlates with poorer prognosis in patients with AIS are complex and multifactorial. An increased ACAG often indicates metabolic acidosis, which may arise from the accumulation of unmeasured anions, such as lactate. This acid-base imbalance adversely affects cellular function and metabolism, leading to further tissue injury[19]. Additionally, elevated levels of unmeasured anions may reflect ongoing metabolic processes due to ischemia, with high lactate levels indicating anaerobic metabolism that exacerbates cerebral ischemia and contributes to neuronal damage[20,21]. Moreover, a high ACAG may signify

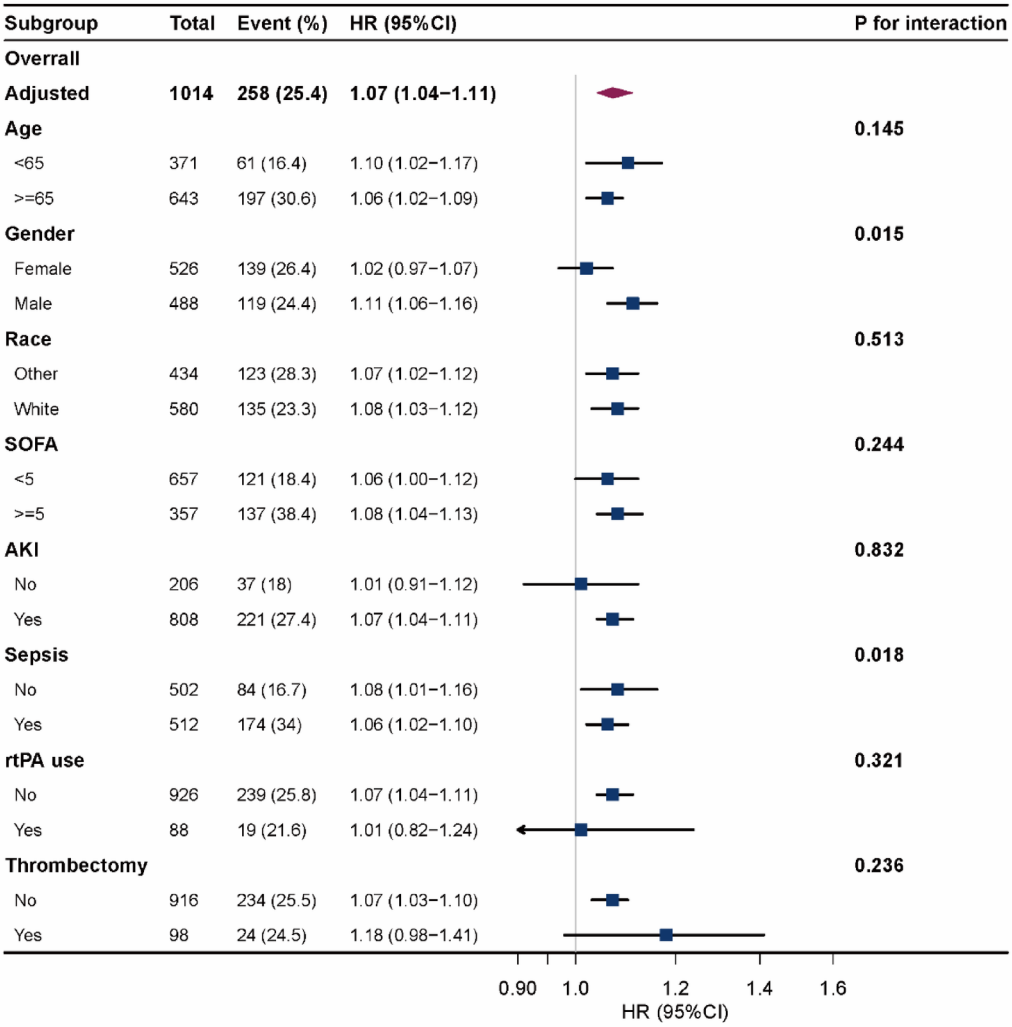

Fig. 5. Association between ACAG and 30-day mortality according to baseline characteristics. Each stratification was adjusted for all factors of Model 3 in Table 3 except for the stratification factor itself. Abbreviations: ACAG, albumin corrected anion gap; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury; rt-PA, recombinant tissue plasminogen activator.

systemic inflammation[8], which is associated with worse outcomes in AIS, as inflammatory mediators can exacerbate brain tissue injury. This elevation may also be linked to oxidative stress, further damaging neuronal cells and impairing recovery.

Subgroup analysis showed a stronger association between ACAG and 30-day mortality in males (HR 1.11, 95% CI 1.06–1.16) than in females (HR 1.02, 95% CI 0.97–1.07). Similarly, the association was stronger in patients without sepsis (HR 1.08, 95% CI 1.01–1.16) compared to those with sepsis (HR 1.06, 95% CI 1.02–1.10). These findings may reflect underlying physiological differences and varying metabolic burdens. Male patients generally have higher metabolic demands and may exhibit a more pronounced response to cardiovascular stress and acid-base imbalance[22,23], which may lead to an increased mortality risk associated with elevated ACAG. In contrast, the metabolic complexity in septic patients, involving multiple inflammatory and metabolic disruptions[24,25], may diminish the predictive utility of ACAG, as other factors such as multi-organ failure likely play a more dominant role in determining outcomes. Additionally, in patients treated with rt-PA or thrombectomy, no significant association was observed between ACAG and mortality. This lack of statistical significance is likely attributable to the limited sample size within these subgroups, as evidenced by the wide confidence intervals. The reduced statistical power in these analyses may have masked potential associations. Future studies with larger cohorts undergoing reperfusion therapies are warranted to further investigate the prognostic utility of ACAG in these specific clinical contexts.

In our study, ACAG demonstrated an independent association with both 30-day and 365-day mortality in AIS patients. However, we acknowledge that the discriminative performance of ACAG alone was modest, with AUCs of 0.666 and 0.662 for 30-day and 365-day mortality, respectively. These values fall within the poor

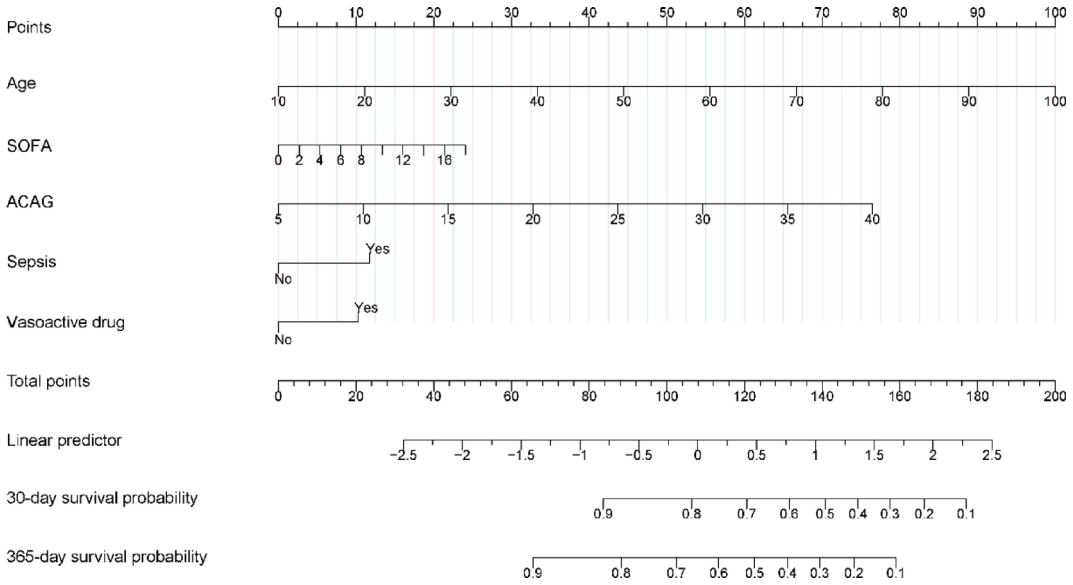

Fig. 6. Nomogram for estimating the risk of mortality in AIS. Abbreviations: SOFA, Sequential Organ Failure Assessment; ACAG, albumin corrected anion gap.

to fair range, indicating that ACAG alone may not serve as a sufficiently strong prognostic tool. Rather, our findings suggest that ACAG functions best as an auxiliary biomarker that enhances risk stratification when used alongside established clinical scoring systems. The combination of ACAG with the SOFA score improved predictive performance, yielding AUCs of 0.691 for 30-day mortality and 0.698 for 365-day mortality, suggesting added value through biochemical-clinical integration. Furthermore, we constructed a nomogram incorporating ACAG and other clinical variables, which further enhanced discrimination, achieving AUCs of 0.748 for 30-day mortality and 0.765 for 365-day mortality. These results support the application of ACAG not as a standalone predictor, but as a component of comprehensive, multimodal prognostic models to aid early identification and management of high-risk AIS patients, particularly in intensive care settings.

These findings suggest that ACAG provides a more comprehensive evaluation of acid-base disturbances in AIS patients than the traditional anion gap. Elevated ACAG reflects metabolic acidosis, which, if uncorrected, may worsen prognosis. Clinically, a high ACAG should prompt evaluation for underlying causes such as lactic acidosis or renal dysfunction and guide timely interventions, including fluid resuscitation, electrolyte correction, or alkalinizing therapy. Given its ease of calculation from standard lab values, incorporating ACAG into routine assessments could aid in early risk stratification and management in both acute and critical care settings.

By focusing on ACAG, we introduce a novel marker of metabolic disturbance that could aid in early risk stratification. However, several limitations should be considered. First, the use of a single ACAG measurement early in hospitalization may not fully reflect dynamic changes over time, which could affect its prognostic utility. Second, the MIMIC-IV database provides only all-cause mortality, without specific information on cardiovascular or stroke-related deaths. This limits our ability to determine whether elevated ACAG is more strongly associated with particular causes of death. The absence of cause-specific data may introduce uncertainty regarding the underlying mechanisms and weaken associations with stroke-specific outcomes. Future prospective studies with detailed mortality classifications are needed to validate our findings and explore the pathophysiological links between ACAG and stroke prognosis. Third, key clinical variables, such as NIHSS scores and brain imaging data, were not included, limiting the assessment of stroke severity and its relationship with ACAG. Moreover, the MIMIC-IV database does not include a detailed classification of stroke subtypes, which could have provided additional insights into whether ACAG levels are associated with specific stroke types or mechanisms. This lack of subtype-specific information limits our ability to explore potential differential effects of ACAG on various stroke subtypes. Further studies incorporating subtype classification are needed to better understand the role of ACAG in AIS prognosis.

In conclusion, elevated ACAG is an independent risk factor for both short-term and long-term mortality in AIS patients. Its incorporation into clinical practice may enhance the ability of clinicians to identify high-risk patients early, enabling timely and targeted interventions.

Data availability

The data supporting the findings of this study were obtained from the MIMIC-IV database(https://mimic.mit.edu/).

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Author contributions

YZ was responsible for Writing - Original Draft. FW, JS, and CX contributed to Formal Analysis, and Software. GW and YQ was involved in Data Curation, Supervision, and Writing - Review & Editing.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The study was conducted in accordance with the principles of the Helsinki Declaration. The data used in this study were obtained from the MIMIC-IV database, which is publicly accessible. Ethical approval for the creation of this database was granted by the Institutional Review Board (IRB) of Beth Israel Deaconess Medical Center (approval number 2001P-001699/14).

Additional information

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